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# Elevated Liver Enzyme Tests Among Rheumatoid Arthritis and Psoriatic Arthritis Patients treated with Methotrexate and/or Leflunomide

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## Abstract

**Introduction—**Potential hepatotoxicity associated with disease modifying anti-rheumatic drugs [DMARDs] requires laboratory monitoring. In rheumatoid and psoriatic arthritis [RA, PsA] patients, we examined the incidence of elevated alanine/aspartate aminotransferase (ALT/AST) enzymes associated with methotrexate (MTX), leflunomide (LEF), and MTX+LEF vs. other DMARDs.

**Methods—**RA and PsA patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) initiating DMARDs were identified. Abnormalities were identified when

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either was 1 or 2-fold time above the upper limits of normal (ULN). Odds ratios [OR] between MTX/LEF dose and elevated ALT/AST enzymes were estimated using generalized estimating equations. Interaction terms for use of MTX+LEF quantified the incremental risk of the combination compared to each individually.

**Results—**Elevated ALT/AST levels (>1× ULN) occurred in 22, 17, 31, and 14% RA patients receiving MTX, LEF, MTX+LEF, or neither, respectively; elevations were 2.76 fold (95% CI 1.84 – 4.15) more likely in PsA patients. Elevations > 2× ULN occurred in 1–2% of patients on MTX or LEF monotherapy compared to 5% with the combination. After multivariable adjustment and compared with either monotherapy, combination MTX + LEF was associated with greater risk according to MTX dose used as part of the combination: MTX 10–17.5mg/week, OR=2.91 (95% confidence interval [CI] 1.23–6.90) and MTX ≥20 mg/week, OR=3.98 (95% CI: 1.72–9.24).

**Conclusions—**14–35% of RA and PsA patients initiating DMARD therapy developed abnormal ALT/AST levels. Risks were incrementally greater in those with PsA and in those receiving MTX (≥ 10mg/day) + LEF. These findings should help inform monitoring for potential hepatotoxicity in these patient populations.

### Keywords

rheumatoid arthritis; psoriatic arthritis; methotrexate; leflunomide; liver function tests; hepatotoxicity

## Introduction

Safety is a common concern among rheumatologists when using non- and biologic-DMARDs in the contemporary era for treatment of rheumatoid (RA) and psoriatic (PsA) arthritis. Previous randomized controlled trials have documented that methotrexate (MTX) or leflunomide (LEF) monotherapy are both associated with a significantly increased incidence of alanine and/or aspartate aminotransferase (ALT and/or AST) elevations [1]. These are predominantly asymptomatic; however, persistent elevations have been shown to correlate with histopathologic changes of fibrosis assessed by liver biopsy with chronic use of MTX [2,3]. Combination use of MTX with LEF has been reported to result in an increased incidence of ALT/AST elevations vs monotherapy with either alone [4], though the effects of medication dose cannot be elucidated because the dose was held fixed by the design of the protocol. The safety of these medications in diseases other than RA, such as psoriatic arthritis, has been less well studied. This knowledge gap is particularly apparent in ‘real world’ settings outside of clinical trials. Moreover, factors such as body mass index (BMI), alcohol consumption, concomitant medications such as NSAIDs, and lack of folic acid supplementation may additionally contribute to transaminase elevations [5–8].

We therefore studied a large cohort of RA and PsA patients receiving MTX, LEF, or both in combination vs neither DMARD to examine the relationship between their use (with a focus on MTX dose) and the incidence of ALT/AST elevations.

## Methods

### Data Source & Study Population

Data from a large cohort of RA and PsA patients receiving care in community and academic settings across the U.S. enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA), were analyzed. Details of this cohort have been previously published [9]. Subjects eligible for analysis were required to have rheumatologist-confirmed diagnosis of RA or PsA and to have initiated treatment with a non-biologic or anti-TNF DMARD; normal

ALT/AST levels were also required at baseline. Individuals with concomitant diagnoses of RA and PsA were also excluded. The observation period extended through April 1st, 2007.

## Drug Exposures

The four categories of DMARD exposure were: 1) MTX, 2) LEF, 3) MTX+LEF, or 4) other non-biologic DMARD combinations excluding MTX and/or LEF, which served as the referent exposure category. The drug exposure categories were mutually exclusive; patients were allowed to change DMARDs over time. Observation time began after initiation of any new DMARD, and patients could contribute exposure time to multiple categories. Use of other non-biologic DMARDs (e.g. hydroxychloroquine, sulfasalazine, gold compounds, azathioprine, or minocycline) and TNF-α inhibitors was permitted in conjunction with each of the four DMARD exposure groups. ALT/AST determinations while patients received biologic DMARDs other than TNF inhibitors (e.g. anakinra, abatacept, rituximab) were excluded from analysis, as were tests when patients were not receiving any DMARDs.

Exposure to one of four DMARD categories at time of ALT/AST determinations was defined as the independent variable of interest; those initiating treatment on the day of liver enzyme tests were included in the analysis of the previous DMARD regimen. Given the prolonged metabolic effects of methotrexate and the long circulating time for leflunomide, patients were included in these categories until they changed exposure categories; a separate sensitivity analysis censored observations at time of treatment discontinuation. Administered MTX and LEF doses in CORRONA are recorded by patients and treating physicians at each clinical encounter. Although 10 and 20 mg daily doses of LEF were initially evaluated, in view of a relatively small number of individuals receiving 10 mg, results for both doses were combined.

## Outcomes of Interest

The primary outcome was any elevation of ALT/AST > upper limits of normal (ULN), using normal cutoff values from a reference laboratory (Covance): ALT: women: 34 (ages 18–69) and 32 (age ≥ 70 years) and men: 43 and 35, respectively; AST, irrespective of age: women: 34 and men: 36. A secondary analysis, examined AST and/or ALT elevations >2× ULN. In both primary and secondary analyses, observation time was censored after the first elevated transaminase level. After identifying patients with new liver function test abnormalities, we then determined the proportion of these people with persistent abnormalities at the next physician visit.

A separate set of sensitivity analyses evaluated patients with at least 2, and at least 3, follow-up visits with lab tests, and additional analyses evaluated the incidence rates of liver function test abnormalities rates using person-time (rather than people) as the denominator to account for varying lengths of follow-up.

## Statistical Analysis

Descriptive statistics were used for all comparisons. Following a determination of per-person incidence of ALT/AST elevations by DMARD exposure category, additional risk factors were included in multivariable analyses. Logistic regression examined relationships between use and dose of MTX, LEF, or MTX+LEF and risk of elevated ALT/AST levels among RA patients. Those receiving non-biologic DMARDs other than MTX and/or LEF served as the reference group. In bivariate analyses, additional factors associated with elevated ALT/AST values with p values < 0.05 were included in multivariable models; covariates of high clinical interest were forced in. A parallel model was created for PsA patients and included as many of the same covariates as possible to facilitate a qualitative comparison with the RA patients. A few covariates, such as LEF use, had to be excluded in models that examined PsA patients due to very low prevalence of use. Generalized estimating equations were used to account for

within-person clustering of study visits. All analyses were performed using STATA version 10 (StataCorp, College Station, TX).

## Results

Of 10,863 CORRONA participants with rheumatoid arthritis (n = 9755) or PsA (n = 1108) with at least one follow-up visit, 5,858 follow-up visits among 2,104 unique patients (n = 1953 RA patients, n = 151 PsA patients) were identified after initiation of a new DMARD and when ALT/AST determinations were performed. The mean time between study visits at which liver function tests were drawn was approximately 5 months. Characteristics of this study population are presented in Table 1. As shown in the third row, between 2 and 12% of the treatment periods were contributed by PsA patients; the remainder were from RA patients. Patients receiving MTX+LEF or MTX monotherapy were less likely to have a history of liver disorder or use daily alcohol, and more likely to receive folate supplements.

Table 2 describes the relationship between per-person incidence of ALT/AST elevations and DMARD exposure. The proportion of RA patients with transaminase elevations was greatest in those receiving MTX+LEF in combination: 31% for any AST or ALT > 1× ULN and 5% for > 2× ULN. In the subgroup of patients with PsA using MTX, this proportion was 35% and was numerically higher than in PsA patients receiving neither MTX nor LEF (28%) [p = 0.18]. Among the PsA patients, there was not enough exposure to LEF (alone, or in combination with MTX) to independently assess this exposure. Sensitivity analyses that evaluated patients that had at least 2 or 3 follow-up visits with lab tests, and those analyses that compared incidence rates by drug exposure, yielded results similar to those in Table 2 (data not shown). The proportion of persons with AST or ALT > 3× ULN was exceedingly small (less than 1%).

After identifying persons with new onset liver function test abnormalities, we then evaluated their persistence. Among persons with new liver function test abnormalities initially >1× ULN, 37% of these persons had abnormalities at the next physician visit. For the persons with new abnormalities > 2× ULN, 48% had abnormalities (>1× ULN) at the next visit.

Factors potentially associated with ALT/AST elevations among RA patients are shown in Table 3. After multivariable adjustment, there was a synergistic effect of combination MTX+ LEF combination, especially with higher doses of MTX. Among several other factors, a past history of liver disorder, and daily alcohol use were associated with ALT/AST elevations. Of interest, there was no significant protective effect of folate supplementation (adjusted odds ratio = 0.97, p = 0.88). Although not significant, trends from the parallel model for PsA patients presented in Table 4 suggested that PsA patients had a greater risk for ALT/AST elevations associated with the use of MTX and with higher BMI. When the data represented in Table 3 and Table 4 were pooled together, PsA patients had a 2.76-fold (95% CI 1.84 – 4.15) greater likelihood of ALT/AST abnormalities after multivariable adjustment. Results from the sensitivity analysis that censored participants at the exact time of MTX, LEF, or other DMARD discontinuation resulted in similar but less precise risk estimates.

## Discussion

In a large cohort of RA and PsA patients receiving MTX, LEF, both in combination, or other non-biologic or TNF inhibitor DMARDs, we observed that increased ALT/AST lab tests were common, In RA patients, the incidence of these abnormalities ranged from 14 – 22% for people on monotherapy alone. With combination MTX+LEF, this proportion was greater: 31%; with a significant dose-response relationship with MTX. Compared with RA, patients with PsA appeared to be at increased risk, as were individuals with a history of pre-existing liver disorder and daily alcohol use.

The incidence of ALT/AST elevations we observed with use of MTX or LEF is comparable to those reported in randomized controlled trials (RCTs), where incidence rates between 5.4% and 16.3% have been reported in the first year after their initiation [10–12]. Additionally, we found that combination therapy with MTX+ LEF increased the incidence of ALT/AST elevations approximately 2–5 fold (depending on MTX dose) vs those receiving either monotherapy. This is consistent with data from a clinical trial of combination MTX+LEF therapy in which a greater than 4-fold increase in liver transaminase elevation was observed with MTX and LEF compared to MTX alone [4]. However, in that trial, the MTX dose was quite constrained by the protocol (to either 15 or 20 mg weekly), precluding evaluation across a wide range of MTX doses. To facilitate comparison between our results and a less select population, a recent report using data from the National Health and Nutrition Evaluation Examination Survey (NHANES) assessed the prevalence of liver enzyme abnormalities in the general U.S. adult population [13]. In contrast to the relatively high proportions that we found and have been previously described for RA and PsA patients, NHANES found that 6% of the population had liver enzyme tests greater than the upper limit of normal; 1% had elevations greater than twice the upper limit of normal.

In multivariable models, the adjusted likelihood of ALT/AST elevations in PsA patients was approximately two to three-fold greater compared to RA patients. This is consistent with concerns suggesting that patients with psoriasis may be particularly sensitive to MTX [8]. In one RCT examining LEF treatment in PsA, the incidence of ALT/AST abnormalities (10.4% over 6 months treatment) was relatively low and comparable to those reported in RA RCTs [14]. In contrast, in a long-term retrospective cohort study of patients with psoriasis and psoriatic arthritis treated with MTX, 78% with PsA, ALT/AST elevations were reported at least once in 57% [15]. Although dissimilarities in study populations and/or follow-up may account for some differences, these observations may also reflect channeling of high risk patients away from more hepatotoxic therapies. This hypothesis is supported by Table 1 which shows that patients receiving MTX and MTX+LEF were less likely to have a history of liver disorders and regular alcohol use and were more likely to use folate supplementation.

The strengths of this study include evaluation of a large number of RA and PsA patients receiving care in routine clinical settings, which allowed focus on interactions between various doses of MTX and LEF. Although previous RA RCTs have reported relationships between DMARD exposures and ALT/AST elevations, risks associated with varying DMARD doses typically have been limited by allowance of only 2 doses of MTX. Thus, a focus on MTX dose contributes to the novelty of our report. Moreover, the safety profile of these DMARDs in PsA patients has been less well studied outside of clinical trials; results from such trials may have limited generalizability to the much broader spectrum of patients treated with these agents in clinical practice.

As a potential limitation of these analyses, a definition of any ALT/AST elevation > ULN is very sensitive. For this reason, elevations >2× ULN were also evaluated. Moreover, any persistent ALT/AST elevations into the abnormal range have been shown to correlate with histopathologic changes on liver biopsy in RA patients [2,3]; these data served as the basis for published guidelines for monitoring of MTX treatment in RA [16], and any elevation may prompt change in therapy or reductions in dose. It has also been shown that patients starting MTX increase the magnitude of their initial normal AST measurements by 2-fold from baseline, even while remaining in the normal range (16). In light of these separate lines of published evidence, we believe that it is somewhat arbitrary to label elevations into the abnormal range of between 1 and 2× normal as uniformly inconsequential. Additionally, monitoring lab tests are not presently mandated by CORRONA, and it may be that patients on potentially hepatotoxic DMARDs have had more follow-up lab tests, resulting in a detection bias. However, our sensitivity analyses that evaluated patients with a minimum number of

follow-up lab tests did not change our results. Additionally, although we considered persons who changed drug treatment groups to remain exposed until they started a new drug, we recognize the possibility that there was a 'carryover' effect from the prior drug therapy. If this were this case, it would have increased the proportion of patients in the non-MTX, non-LEF exposure group with ALT/AST elevations; however, this effect would serve only to attenuate our results towards the null. Finally, we acknowledge that results from this U.S. cohort may not be generalizable to individuals receiving care in other settings where, for example, the prevalence of alcohol use and other hepatotoxic agents may differ.

In conclusion, the proportion of RA patients with ALT/AST elevations >ULN cared for in routine clinical practice in the US CORRONA registry receiving MTX or LEF was approximately 14–22%, and greater for those receiving combination MTX+LEF, particularly at doses of MTX ≥ 10 mg/week. We have documented what appears to be a selection bias of high risk patients away from therapeutic regimens which may be associated with more hepatotoxicity. We also have shown that liver enzyme test abnormalities were numerically more frequent in PsA patients. These data support the need for continued careful monitoring of transaminase enzymes in patients with both RA and PsA who receive treatment with either MTX, LEF, or the combination.

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## Table 1

Baseline Characteristics of CORRONA Cohort Newly Initiating a DMARD with at least 1 follow-up visit (n = 2,104 unique persons), by Drug Exposure

| Drug Exposure | MTX + LEF | MTX | LEF | No MTX or LEF |
|---|---|---|---|---|
| Number of treatment periods* | 103 | 1342 | 157 | 502 |
| Anti-TNF Use, % | 27.2 | 54.9 | 42.0 | 75.1 |
| PsA diagnosis**, % | 1.9 | 6.2 | 3.8 | 12.0 |
| Age (yrs) | 58.8 +- 12.8 | 59.1 +- 13.3 | 59.4 +- 14.4 | 56.9 +- 14.9 |
| Duration of Disease (yrs) | 12.9 +- 11.4 | 10.8 +- 9.8 | 11.0 +- 8.8 | 11.9 |
| Female, % | 80.6 | 74.0 | 78.3 | 70.9 |
| White, % | 83.5 | 84.7 | 85.9 | 82.4 |
| Private Insurance, % | 76.6 | 76.6 | 72.4 | 78.0 |
| Medicare Insurance, % | 42.9 | 37.5 | 45.7 | 37.1 |
| Medicaid Insurance, % | 13.0 | 5.8 | 5.5 | 6.9 |
| Current smoker, % | 18.6 | 15.3 | 23.5 | 15.5 |
| Body mass index | 28.7 +- 7.0 | 29.3 +- 7.1 | 27.9 +- 6.2 | 29.2 +- 7.5 |
| Diabetes, % | 6.8 | 6.3 | 10.2 | 6.8 |
| Liver Disorder, % | 6.8 | 3.7 | 7.0 | 9.2 |
| Number of prior other non-biologic DMARDs | 0.6 ± 0.8 | 0.8 ± 1.1 | 0.7 ± 1.0 | 0.8 ± 1.0 |
| Use of Folic acid, % | 76.6 | 76.6 | 28.4 | 23.6 |
| Use of a Cholesterol Medication, % | 18.2 | 16.3 | 20.5 | 15.1 |
| Use of an NSAID, % | 46.6 | 45.1 | 44.6 | 48.0 |

| Drug Exposure | MTX + LEF | MTX | LEF | No MTX or LEF |
|---|---|---|---|---|
| Drinking alcohol, % | | | | |
| None or occasional | 77.8 | 78.0 | 69.9 | 68.1 |
| 1–3 drinks per week | 20.2 | 18.2 | 22.6 | 25.3 |
| 1–2 per day | 2.0 | 3.9 | 7.5 | 6.6 |
| ≥ 3 per day | 0.0 | 0.4 | 0.7 | 0.8 |
| Daily prednisone dose | 54.5 | 65.2 | 56.4 | 66.7 |
| None | 17.8 | 12.8 | 11.5 | 9.8 |
| < 5 mg | 21.8 | 15.2 | 19.2 | 15.0 |
| 5–10 mg | 5.9 | 6.8 | 12.8 | 8.4 |
| ≥ 10 mg | | | | |
| **Health Services Utilization during observation period after drug initiation** | | | | |
| Number of follow-up visits, mean | 2.9 ± 2.5 | 3.7 ± 2.6 | 3.4 ± 2.9 | 3.2 ± 2.5 |
| Number of follow-up visits with liver enzyme tests available | 2.3 ± 1.1 | 2.1 ± 1.0 | 2.2 ± 1.0 | 1.8 ± 1.0 |

Data are shown as proportions or mean ± standard deviation

* a treatment period indicates that a person was newly exposed to this drug or drug combination

** reflects the proportion of treatment periods contributed by patients with psoriatic arthritis; the remainder of the treatment periods were contributed by rheumatoid arthritis patients

## Table 2

Proportion of Follow-up Visits with Laboratory Tests Available at Which Elevated Liver Enzyme Tests* Were Identified, by Disease and Drug Exposure

| | RA Patients (n = 1953) | | PsA Patients (n = 151) | |
|---|---|---|---|---|
| | **Proportion with AST or ALT > 1× ULN, %** | **Proportion with AST or ALT > 2× ULN, %** | **Proportion with AST or ALT > 1× ULN, %** | **Proportion with AST or ALT > 2× ULN, %** |
| Methotrexate alone, % | 22 | 1 | 35 | 0 |
| Leflunomide alone, % | 17 | 2 | - | - |
| Methotrexate + leflunomide, % | 31 | 5 | - | - |
| Neither methotrexate nor leflunomide, % | 14 | 2 | 28 | 3 |
| *P value for column* | < 0.01 | < 0.01 | NS | NS |

ULN = upper limit of normal; NS = Not significant; - indicates fewer than 10 PsA patients were on this treatment regimen

* Defined as AST or ALT greater than 1× or 2× times the upper limit of the laboratory normal (ULN)

## Table 3

Adjusted* Relationship between Selected Risk Factors for Elevated Liver Enzyme Tests among Rheumatoid Arthritis Patients**

| Covariate | OR (95% CI) |
|---|---|
| **Methotrexate (mg/week)** | |
| None | 1.0 (referent) |
| 2.5 – 7.5 | 1.33 (0.88 – 1.99) |
| 10 – 17.5 | 1.11 (0.76 – 1.62) |
| ≥ 20 | 1.41 (0.96 – 2.08) |
| **Leflunomide** | |
| None | 1.0 (referent) |
| Any dose | 0.83 (0.63 – 1.77) |
| **Additional MTX + leflunomide interaction†** | |
| No concomitant use | 1.0 (referent) |
| 2.5 – 7.5 mg MTX + Arava | 2.15 (0.79 – 5.85) |
| 10 – 17.5 mg MTX + Arava | 2.91 (1.23 – 6.90) |
| ≥ 20 mg MTX + Arava | 3.98 (1.72 – 9.24) |
| **Anti-TNF use (referent to no use)** | 1.15 (0.90 – 1.47) |
| **Body mass index** | |
| < **25** | 1.0 (referent) |
| **25–30** | 1.21 (0.90 – 1.61) |
| **> 30** | 1.22 (0.92 – 1.62) |
| **Current Tobacco use** | 0.58 (0.40 – 0.82) |
| **History of liver disorder** | 2.07 (1.38 – 3.08) |

| Covariate | OR (95% CI) |
|---|---|
| Number of liver enzyme test blood draws‡ | 1.26 (1.05 – 1.52) |
| **Alcohol use** | |
| None / occasional | 1.0 (referent) |
| 1–3 / week | 0.97(0.72 – 1.31) |
| 1–2 / day | 1.97 (1.18 – 3.28) |

OR = Odds Ratio; BMI = body mass index

*additional covariates adjusted for but which were not significant included age, gender, duration of disease, number of physician visits, glucocorticoid dose, NSAID use, recent hospitalization, and folate supplementation

**Defined as AST or ALT greater than the upper limit of the laboratory normal

†quantifies the incremental risk of using both MTX and LEF together, on top of the risk of using each alone

‡during observation period

## Table 4

Adjusted* Relationship between Selected Risk Factors for Elevated Liver Enzyme Tests among Psoriatic Arthritis Patients**

| Covariate | OR (95% CI) |
|---|---|
| **Methotrexate (mg/week)** | |
| None | 1.0 (referent) |
| 2.5 – 7.5 | 1.23 (0.25 – 5.9) |
| 10 – 12.5 | 3.04 (0.70 – 13.29) |
| ≥ 15 | 2.37 (0.81 – 6.92) |
| **Anti-TNF use (referent to no use)** | 0.82 (0.31 – 2.17) |
| **Body mass index** | |
| **< 25** | 1.0 (referent) |
| **25–30** | 2.97 (0.77 – 11.41) |
| **> 30** | 3.09 (0.84 – 11.45) |
| **Current Tobacco use** | 1.35 (0.40 – 4.55) |
| **History of liver disorder** | 4.96 (0.95 – 25.90) |
| Number of liver enzyme test blood draws*** | 1.22 (0.53 – 2.84) |
| **Alcohol use** | |
| None / occasional | 1.0 (referent) |
| 1–3 / week | 1.22 (0.46 – 3.24) |
| ≥ 1 / day | 2.18 (0.52 – 9.15) |

OR = Odds Ratio; PsA = psoriatic arthritis; RA = rheumatoid arthritis; BMI = body mass index

* similar to Table 3, additional covariates adjusted for included age, gender, duration of disease, number of physician visits, NSAID use, recent hospitalization, an interaction term between PsA and alcohol, and folate supplementation

** Defined as AST or ALT greater than the upper limit of the laboratory normal

*** during observation period